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Increased QT dispersion and related factors in patients with systemic sclerosis

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ABSTRACT

Introduction: Cardiac arrhythmias and sudden death may occur as a result of ventricular myocardial fibrosis or ischemia in patients with systemic sclerosis (SSc). QT prolongation and QT dispersion, which facilitate the development of ventricular fibrillation, are important cardiac problems associated with increased mortality. In this study, we aimed to investigate the prevalence of corrected QT dispersion (cQTD) and related factors in our patients with systemic sclerosis compared to healthy controls.

Material and Method: The 12-lead electrocardiograms with a rate of 25 mm/s of patients with no previous history of cardiovascular disease and controls were analyzed. cQTD was defined as the difference between the maximum QT interval and the minimum QT interval. Nailfold capillaroscopy examination was performed. Disease activity was evaluated using revised European Scleroderma Study Group activity index.

Results: Forty-nine SSc patients (45 females, mean age 53.26±10.63 years, and disease duration 8.0 (1-25) years) and 41 controls (37 females, mean age 49.29±8.02 years) were included. While the frequency of smoking was significantly higher in controls ($p=0.025$), erythrocyte sedimentation rate was higher in patients ($p<0.001$). cQTD was significantly higher in the patient group compared to the control group (65.14±17.57 ms and 42.73±10.03 ms, respectively, $p<0.001$). A significant positive correlation was found between erythrocyte sedimentation rate and cQTD in the patient group. We found no association between cQTD and disease activity, medications, anti-SSA/Ro positivity, capillaroscopy paterns, presence of interstitial lung disease and pulmonary arterial hypertension.

Conclusion: In our study, cQTD, which indicates an increased risk for ventricular arrhythmia and cardiovascular mortality, was found to be significantly higher in the patients compared to the controls. Determining cardiac risks with an electrocardiogram, which is a non-invasive and easily available method, is important in the follow-up of SSc patients.

Keywords: Systemic sclerosis, cardiovascular mortality, QT dispersion

INTRODUCTION

Systemic sclerosis (SSc) is a chronic autoimmune disease characterised by extensive fibrosis of the skin and internal organs (1). It is thought to be developed as a result of interactions between factors affecting collagen synthesis, vascular changes, and immunological mechanisms. The fibrotic changes in diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc), which are the subgroups of SSc, are not limited to the skin but also in internal organs (2). While skin changes and contractures affect morbidity, internal organ involvement significantly affects both morbidity and mortality.

Cardiac involvement in SSc patients is mostly asymptomatic; therefore its exact prevalence is unknown. Myocardial fibrosis and pericardial disease, the main pathogenic features of cardiac involvement in SSc, are present in approximately 80% of the patients at autopsy reports (3). When clinical signs are present (10-35% of the patients with SSc), the prognosis is generally poor, with a 5-year mortality rate of approximately 70% (4). Heart blocks, atrial or ventricular arrhythmias can be seen in approximately 50% of the patients. Ventricular arrhythmia is the most common cause of death in patients with SSc after pulmonary fibrosis and pulmonary hypertension (5). The QT prolongation, an important cause of cardiac arrhythmias, can be detected in electrocardiography (ECG), which is an easy and non-invasive method. The QT prolongation is also seen

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in patients with SSc and can lead to life-threatening arrhythmias and even sudden cardiac death. Sudden cardiac death occurs in 5% of patients with SSc, and arrhythmias cause 6% of all-cause mortality in SSc (5). The prevalence of the QT prolongation in SSc has been shown to be 11-25% in previous studies (6, 7). Therefore, it is important to detect QT prolongation in SSc patients with high-risk. QT dispersion (QTd) is a marker of repolarization heterogeneity reported to be linked to an increased rate of arrhythmias (8). However, whether increased QTd is more common in SSc is still debated (9).

In this study, we aimed to investigate the prevalence of corrected QT dispersion (cQTD) and related factors in our patients with SSc compared to healthy controls.

MATERIAL AND METHOD

This study was carried out with the permission of Manisa Celal Bayar University Medical Faculty Clinical Researches Ethics Committee (Date: 30.03.2022, Decision No: 20.478.486/1283). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this cross-sectional study, 49 SSc patients who applied to our rheumatology outpatient clinics between March 2021 and March 2022 and 41 healthy controls with similar demographic characteristics as the patient group were included. According to the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2013 criteria, the patients with a score of 9 and above were classified as SSc (10). Patients with diabetes mellitus, hypertension, dyslipidemia, chronic renal failure, chronic liver disease, known coronary artery or structural heart disease, rhythm abnormalities were excluded. Patients using antiarrhythmic agents such as digitalis, and beta blockers were also not included. The SSc patients and healthy controls gave informed written consent.

Demographic information including age and sex of the study population, the clinical evaluation including a detailed medical history and physical evaluation of SSc patients were recorded. Disease duration was defined as the time from the onset of the first sign of disease to the baseline study visit, excluding raynaud's phenomenon. Body mass index (BMI), systolic and diastolic blood pressure were measured. The presence of SSc specific features such as raynaud's phenomenon, digital ulcer, gangrene, sclerodactyly, arthralgia, arthritis, tendon friction rubs, gastroesophageal reflux, diarrhea, cough, shortness of breath were also recorded. Skin involvement was assessed with the Modified Rodnan skin severity score (MR-SSS) involving the degree of skin thickening ranging from 0 (noinvolvement) to 3 (severe thickening) in 17 areas of the body (total score range: 0–51) (11). Patients were classified as limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the definition of Leroy et al (12). Tendon friction rubs, arthritis, myositis were determined as musculoskeletal system involvement. Nailfold capillaroscopy examination was performed to detect capillary changes indicating microvascular damage. The patients were classified as having early, active and late SSc patterns according to the capillaroscopy examination findings.

Complete blood count and biochemical markers (fasting blood glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), electrolytes, total protein, albumin, lipids) erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) of whole study population were analyzed on the date ECG performed. In the SSc group, the most recent antibody test results were recorded from the hospital database.. Anti-nuclear antibodies (ANA) of the patients were examined by indirect fluorescent antibody (IFA) (hep-2 cells) and other antibodies including anti-centromere antibodies, anti-Scl-70, SSA/Ro, SSB/La, anti-Sm-RNP were measured by ELISA (enzyme linked immunosorbant assay) ELISA method. ANA titer above 1/160 was considered significant. ANA test was performed in healthy controls during the study and ANA positive controls were excluded.

In our rheumatology outpatient clinic, all SSc patients undergo routine follow-up tests such as echocardiogram, high-resolution computed tomography (HRCT), and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide (DLCO), at least once a six mounths. The latest findings of these tests were obtained from hospital records. Detection of at least one pathological pulmonary parenchymal finding including ground glass changes, honeycombing, subpleural opacity on HRCT was accepted as interstitial lung disease (ILD). Pulmonary artery pressure (PAP) ≥35 mmHg on echocardiography was accepted as pulmonary arterial hypertension (PAH). Disease activity was evaluated using revised the European Scleroderma Study Group (EScSG) activity index (13). The patients with a cut-off points ≥2.5 was accepted to have active disease (13).

Electrocardiogram and Measurement of Indices

A 12-lead ECG were recorded in the resting supine position using a commercial machine (GE Healthcare, MAC 2000) at a rate of 25 mm/s. ECG images were amplified 200%, and measurements were taken blindly in an electronic setting by the same person utilizing

manual ECG reading. The distance from the beginning of the QRS complex to the end of the T wave was measured as the QT interval. QTD was defined as the difference between the maximum QT interval and the minimum QT interval in any lead on a standard 12-lead ECG. cQTD was calculated with Bazett's formula (cQTD=QT interval / RR interval square root). Greater than or equal to 440 ms of cQTmax was accepted as prolonged QTc (14).

Statistical Analysis

Statistical analysis was performed using the Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA) 22.0 package program. Quantitative variables were expressed as mean±standard deviation (SD) or median (minimum and maximum), as appropriate. and qualitative variables were presented as numbers and percentages. In the statistical analysis of continuous data, normality of distribution was assessed using Kolmogorov-Smirnov test. The independent samples T-test or Mann-Whitney U test were used to compare numerical data between independent groups, while Pearson's chi-square or Fischer's exact test were used to compare categorical variables. When comparing continuous data between more than two subgroups, the ANOVA test was used for those with normal distribution, and the Kruskal-Wallis test for those without normal distribution. The correlation analysis between ECG variables and disease duration, laboratory values and disease activity parameters were evaluated with Pearson correlation analysis for variables showing normal distribution and Spearman correlation analysis for variables not showing normal distribution. At the level of $p \leq 0.05$, all results were considered statistically significant.

RESULTS

A total of 49 SSc patients and 41 healthy controls were included in the study. There was no statistical difference between the mean age of the SSc group (53.26±10.63) and the control group (49.29±8.02) (p>0.05). The frequency of smoking was significantly higher in controls (p=0.025). Erythrocyte sedimentation rate (ESR) was higher in SSc patients (p<0.001). Comparison of other demographic, clinical, and laboratory characteristics of the groups were summarized in **Table 1**.

Electrocardiographic parameters of the groups are also shown in **Table 1**. Maximum corrected QT (cQTmax) and cQTD intervals were significantly higher in the SSc group compared to the control group (cQTmax: 440.85±29.86 ms vs 411.92±33.06 ms and cQTD: 65.14±17.57 ms vs 42.73±10.03 ms). cQTmax was found to be higher than 440 ms in 41% of the patients have prolonged QTc

Table 1. Comparison of demographic, clinical, laboratory, and electrocardiographic variables between SSc patients and healthy controls

Variables	SSc (n=49)	Control (n=41)	p
Age (years)	53.26±10.63	49.29±8.02	0.052
Female (n, %)	45 (91.2%)	37 (90.2%)	0.791
Smoker (n, %)	7 (14.3%)	15 (36.6%)	0.025
BMI	25.81±4.97	26.00±3.06	0.824
Systolic BP (mm Hg)	118.73±13.45	115.25±15.20	0.254
Diastolic BP (mm Hg)	73.23±8.54	75.22±7.43	0.340
Haemoglobin (g/dL)	12.48±1.59	12.80±1.25	0.303
WBC (10^3/μL)	8.82±2.63	7.61±2.05	0.233
Creatinine (mg/dl)	0.62±0.25	0.64±0.14	0.654
ALT (U/L)	23.06±12.07	22.54±14.52	0.784
Glucose (mg/dl)	99.81±30.12	89.94±10.62	0.078
LDL-cholesterol (mg/dL)	110.05±20.65	108.00±18.81	0.299
HDL-cholesterol (mg/dL)	45.12±11.82	53.00±12.71	0.078
Triglyseride (mg/dL)	166.45±35.66	168.41±26.78	0.559
ESR (mm/hour)	34.18±25.12	15.95±8.96	<0.001
CRP (mg/dL)	1.82±3.10	0.98±0.91	0.107
Heart rate (beats/min)	78.15±13.73	76.34±9.19	0.487
cQTmax (ms)	440.85±29.86	411.92±33.06	0.001
cQTmin (ms)	373.79±30.23	373.12±29.08	0.916
cQTD (ms)	65.14±17.57	42.73±10.03	<0.001

SSc: Systemic sclerosis, BMI: Body mass index, Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, WBC: White blood cell, ALT: Alanine Aminotransferase, LDL-cholesterol: low-density lipoprotein- cholesterol, HDL-cholesterol: High-density lipoprotein-cholesterol, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, cQTmax: Corrected QT maximum, cQTmin: Corrected QT minimum, cQTD: Corrected QT dispersion

Twenty-one (42.8%) of the SSc patients were classified as lcSSc and 28 (57.2%) of them as dcSSc. The median diagnosis duration of the patients was calculated as 8 (1-25) years. The most common clinical finding in SSc patients was raynaud's phenomenon (92%). The clinical features of patients with lcSSc and dcSSc were given in a **Table 2**. The medications used in the SSc group were acetylsalicylic acid (67.3%), proton pump inhibitor (71.4%), calcium channel blocker (30.6%), bosentan (18.3%), corticosteroid (48.9%), hydroxychloroquine (26.5%), and immunosuppressive agents (azathiopurine, mycophenolate mofetil, methotrexate) (26.5%).

ANA was positive in 49 (100%) patients with SSc. The number of patients with positive anti-centromere antibody and anti-Scl-70 antibody were 9 (18.3%) and 28 (57.2%), respectively. Other antibodies found to be positive were anti-SSA (8.1%), anti-SSB (4.1%), and anti-Sm-RNP (8.1%). No ANA positivity was detected in the control group. According to the capillaroscopy patterns, SSc patients were classified as early (22.4%), active (44.8%) and late (32.4%).

In subgroup analyses, there were no significant differences in terms of ECG parameters between diffuse and limited SSc subgroups (p>0.05) (**Table 2**). There were no significant differences in QT intervals between early, active, and late SSc groups (p>0.05). The association of cQTD with smoking status, disease activity, medications,

anti-SSA/Ro positivity, capillaroscopy paterns, presence of ILD and PAH, involvement of musculoskeletal and gastrointestinal systems were summarized in **Table 3**.

Table 2. The clinical and electrocardiographic features of patients with lcSSc and dcSSc.

Variables	lcSSc (n=21)	dcSSc (n=28)	All patients (n=49)	p
Age (years)	52.9±9.8	53.5±10.2	53.2±10.5	0.861
Female (n,%)	21 (100)	24 (85.7)	45 (91.8)	0.071
Diagnosis duration (years)	10.0 (3-25)	6.5 (1-20)	8.0 (1-25)	0.060
ILD (n,%)	4 (19)	21 (75)	25 (51)	<0.001
PAH (n,%)	3 (14.3)	5 (17.9)	8 (16.3)	0.100
GIT involvement (n,%)	13 (61.9)	21 (75)	34 (69.3)	0.363
MSK involvement (n,%)	11 (52.4)	16 (57.1)	27 (55.1)	0.779
Digital ulcer (n,%)	2 (9.5)	4 (14.3)	6 (12.2)	0.688
MR-SSS	17.9±11.4	26.2±13.0	22.6±12.9	0.025
FVC (%)	81 (70-88)	71 (65-89)	75 (65-89)	0.002
DLCO (%)	71 (65-74)	68 (60-72)	70 (60-74)	<0.001
EScSG activity index	1.50 (0-6.25)	2.5 (0-6.25)	2.5 (0-625)	0.028
Heart rate (beats/min)	78.47±12.17	77.39±14.95	78.15±13.73	0.564
cQTmin (ms)	375.04±30.35	372.21±30.35	373.79±30.23	0.887
cQTmax (ms)	440.45±30.46	440.95±28.76	440.85±29.86	0.991
cQTD (ms)	64.71±16.45	66.85±18.41	65.14±17.57	0.675

lcSSc: limited cutaneous systemic sclerosis, dcSSc: diffuse cutaneous systemic sclerosis, ILD: Interstitial lung disease, PAH: Pulmonary arterial hypertension, GIT involvement: Gastrointestinal tract involvement, MSK involvement: Musculoskeletal involvement, MR-SSS: Modified Rodnan skin severity score, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, EScSG activity index: European Scleroderma Study Group activity index, cQTmax: Corrected QT maximum, cQTmin: Corrected QT minimum, cQTD: Corrected QT dispersion

Table 3. The association of cQTD with clinical and laboratory features of SSc

Variables		n	cQTD	p
Smoking	Yes	7	58.28±19.14	0.281
	No	41	66.24±17.15	
Active disease (EScSG index ≥2.5)	Yes	28	66.71±16.50	0.414
	No	21	62.57±18.79	
Hydroxychloroquine	Yes	13	64.77±11.81	0.968
	No	36	65.00±19.23	
Corticosteroid	Yes	24	65.30±15.06	0.981
	No	25	65.88±19.78	
Calcium channel blocker	Yes	15	63.66±13.06	0.739
	No	34	65.56±19.22	
anti-SSA/Ro	Positive	4	64.25±19.80	0.935
	Negative	45	65.15±17.47	
Interstitial lung disease	Yes	25	66.92±19.38	0.423
	No	24	62.97±15.32	
Pulmonary arterial hypertension	Yes	8	68.87±16.55	0.491
	No	41	64.17±17.71	
Capillaroscopy paterns	Early	11	62.00±23.43	0.053
	Active	22	63.45±13.97	
	Late	16	69.00±17.54	
Musculoskeletal involvement	Yes	27	67.62±19.30	0.236
	No	22	61.63±14.62	
Gastrointestinal involvement	Yes	34	66.82±18.07	0.259
	No	15	60.66±15.68	
Digital ulcer	Yes	6	63.60±17.59	0.154
	No	43	74.50±14.12	

cQTD: Corrected QT dispersion, SSc: Systemic sclerosis, EScSG activity index: European Scleroderma Study Group activity index.

When correlation analysis was performed, no correlation was found between disease duration, BMI, and cQTmax and cQTD (p>0.05). There was significant correlation between cQTmax and creatinine level (p=0.002, r =0.430) and between ESR and cQTD (p= 0.019, r =0.334) in the SSc group. The mean MR-SSS indicating severity of skin involvement was 22.67±12.92 in the SSc patients, and no correlation was found between MR-SSS and QT interval parameters. A significant correlation was found between cQTmin and antibody level in 4 patients with positive anti-SSA (P=0.017, r=0.340). There was no significant correlation between ECG parameters and PAB, left ventricle ejection fraction and EScSG activity index in the patient group (p>0.05). Correlation analysis between cQTD and variables of some clinical and laboratory features of SSc patients are shown in **Table 4**.

Table 4. Correlation analysis between cQTD and variables of some clinical and laboratory features of SSc patients.

Variables	r	p
Age (year)	0.182	0.087
Disease duration (year)	0.190	0.191
BMI (kg/m²)	-0.104	0.323
Systolic BP (mmHg)	0.201	0.195
Diastolic BP (mmHg)	0.127	0.354
ESR (mm/h)	0.334	0.019
CRP (mg/L)	-0.138	0.193
Albumin (g/dL)	-0.156	0.142
LDL-cholesterol (mg/dL)	0.109	0.554
HDL-cholesterol (mg/dL)	-0.169	0.238
Triglyseride (mg/dL)	0.226	0.121
MR-SSS	0.103	0.482
FVC (%)	-0.215	0.138
DLCO (%)	-0.165	0.257
PAP (mm Hg)	0.074	0.615
LVEF (%)	-0.181	0.212
EScSG activity index	0.239	0.098

cQTD: Corrected QT dispersion, SSc: Systemic sclerosis, BMI: Body mass index, Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, LDL-cholesterol: low-density lipoprotein- cholesterol, HDL-cholesterol: High-density lipoprotein-cholesterol, MR-SSS: Modified Rodnan skin severity score, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, PAP: Pulmonary artery pressure, LVEF: Left Ventricular Ejection Fraction, EScSG activity index: European Scleroderma Study Group activity index.

DISCUSSION

In this study, cQTD, which is an important indicator of ventricular arrhythmia, was found to be significantly higher in patients with SSc than in healthy controls. In the patient group, no association was found between clinical findings, disease duration, BMI, smoking status, capillaroscopy findings, MR-SSS, medications, and electrocardiographic findings. However, a significant positive correlation was found between ESR and cQTD in the SSc group.

Cardiac involvement occurs late in the course of the disease in patients with SSc and is associated with a poor

prognosis. In these patients, the frequency of ventricular ectopic beats increases and ventricular tachycardia attacks may be seen. These findings are thought to be the result of fibrosis or ischemia of the ventricular myocardium. Few studies investigating cardiac involvement in SSc patients have evaluated the prevalence and markers of ventricular arrhythmias (15). The presence of cardiac involvement of SSc patients can be detected by ECG, which is an easy and inexpensive method. For this purpose, Çiftçi et al. (16) examined heart rate and QT intervals in dcSSc by using 24-hour ambulatory ECG recording and found that a significant proportion of these patients had QT prolongation.

In the standard 12-lead ECGs, cQT values above 440 ms are considered to be higher than normal. In our study, the mean cQTmax value was 440.85±29.86 ms in SSc patients, and it was found to be higher than 440 ms in 41% of the patients. Massie et al. reported a prolonged cQT interval (422.4±47.10 ms) in 25% of their cohort of 689 SSc patients (17). Although there is no consensus, the normal range of cQTD is reported from 31±11 ms to 54±27 ms. A 50ms increase in the QT interval is shown to be associated with an increase in mortality (18). In our study, the mean cQTD was measured as 65.14±17.57 in the SSc group and was found to be significantly higher than in the control group.

In a study evaluating SSc patients without cardiac symptoms, it was reported that 14.6% of the patients had prolonged QTc. In addition, it was found that patients with dcSSc subtype had longer QT interval and patients with longer QT interval had higher MR-SSS (19). Similarly, in another study, a significant correlation was found between electrocardiographic ventricular repolarization indices and MR-SSS values in patients with SSc (20). Therefore, they recommended that patients with higher scores had to be followed closely for cardiac arrhythmias. Rosato et al. (21) reported that the presence of active capillaroscopic changes and digital ulcers were associated with higher QTc. However, in our study, no association was found between the disease subtypes, skin scores, capillaroscopic findings, and ECG findings. When different connective tissue diseases were examined, it was reported that there was a relationship between QTD prolongation and the development of complex ventricular arrhythmias in patients with anti-SSA positivity (22). In our study, there was no significant association between cQTD and anti-SSA positivity. We found a significant correlation between ESR, which is an indicator of disease activation in connective tissue diseases, and QTD in patients with SSc. This suggests that many biomarkers of ongoing systemic inflammation may be useful in determining the risk of arrhythmia in these patients.

Our main limitation is that some data including pulmonary function tests, HRCT and echocardiography findings were obtained retrospectively from patient's records. The lack of extensive cardiological evaluation (an objective test to detect the presence of coronary artery disease or detailed echocardiographic examination) by the same cardiologist in patients is another limitation. Manual calculation of QT measurements can also be seen as a limitation. However, taking blindly measurements by the same clinician shows that the difference between the groups is valuable.

CONCLUSION

In conclusion, the evaluation of QT dispersion in the prediction of cardiac arrhythmia and therefore sudden cardiac death with ECG, which is a noninvasive and inexpensive method, will be useful in the follow-up of patients with SSc. However, more comprehensive prospective studies and long-term follow-up are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Manisa Celal Bayar University Medical Faculty Clinical Researches Ethics Committee (Date: 30.03.2022, Decision No: 20.478.486/1283).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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